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Pharmacologic Management of Posttraumatic Stress Disorder

Matthew J. Friedman, MD, PhD

Focus Points

- The empirical evidence on efficacy of psychotropic medications in the treatment of posttraumatic stress disorder (PTSD) symptoms are reviewed.
- A general approach to pharmacotherapy for PTSD is presented.
- Potential adverse side effects associated with medication treatment are reviewed.

Abstract

What are the best medications for posttraumatic stress disorder (PTSD)? The selective serotonin reuptake inhibitors (SSRIs) paroxetine and sertraline have received Food and Drug Administration approval for the treatment of PTSD due to efficacy shown in clinical trials. Although research with other classes of medications has been less extensive, there is currently a fair amount of preliminary information to guide clinician choices for PTSD treatment. This review considers the following classes of medications: SSRIs, newer antidepressants, monoamine oxidase inhibitors, tricyclic antidepressants, antiadrenergics, anticonvulsants, benzodiazepines, and conventional and atypical antipsychotics. At this time, SSRIs are recommended as first-line treatments for PTSD. Evidence favoring other medications is mixed. Current data suggests that there is no indication for prescribing either benzodiazepines or conventional antipsychotic agents for PTSD.

Psychopharmacologic Management of PTSD

Since its introduction as a formal diagnosis in 1980[1], posttraumatic stress disorder (PTSD) has been shown to have a lifetime prevalence of 8% in the United States,[2] with a much higher prevalence in countries affected by civil war, genocide, forced migration, and terrorism.[3] Furthermore, evidence continues to accumulate indicating that in addition to its public health significance as a prevalent psychiatric disorder, PTSD is a risk factor for many medical illnesses.[4]

The last decade has been marked by an increase in clinical trials on both pharmacologic and psychosocial treatments for PTSD, culminating in a practice guideline developed by the International Society for Traumatic Stress Studies (ISTSS).[5] It is an exciting time to consider psychopharmacologic management of PTSD. Two medications, paroxetine and sertraline, both selective serotonin reuptake inhibitors (SSRIs), have already received Food and Drug Administration approval for the treatment of PTSD. Other candidate medications are being tested in multi-site treatment trials. Expanding our knowledge of biological alterations associated with PTSD promises to open the way for the developing and testing of new compounds and our growing understanding of the normal human response to traumatic stress has begun to generate interest in pharmacologic interventions for acutely traumatized individuals.[6-8]

In addition to a number of recent reviews on pharmacotherapy for adults and children,[9] practice guidelines are currently being developed by the American Psychiatric Association and jointly by the US Departments of Veterans Affairs and Defense. These will update the first practice guidelines developed by ISTSS which recommend SSRIs as first-line treatments and other antidepressants as second-rank medications for PTSD.[10]

This article will review results from clinical trials on pharmacotherapy for PTSD in order to equip practitioners with the latest evidence-based information on the relative efficacy of medications currently used in psychiatric practice.

Results From Clinical Trials

Selective Serotonin Reuptake Inhibitors

Sertraline and paroxetine have received FDA approval for the treatment of PTSD based on positive findings in large multisite trials.[11-14] These agents offer many benefits (Table).[15] They are broad spectrum medications which ameliorate symptoms from all three PTSD symptom clusters as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[16]: re-experiencing, avoidant/numbing, and hyperarousal symptoms. They also have proven efficacy against other major *DSM-IV* psychiatric disorders that are frequently comorbid with PTSD, such as depression, panic disorder, social phobia, and obsessive-compulsive disorder. Sertraline and paroxetine also appear to promote reduction of clinically significant symptoms that are often associated with PTSD, such as suicidal, aggressive, and impulsive behavior. Finally, as with all SSRIs, their side-effect profile is relatively benign compared to other medications. A large multisite trial and smaller open trials with fluoxetine indicate

Dr. Friedman is executive director at the National Center for Posttraumatic Stress Disorder at the Veteran's Affairs Medical and Regional Office Center in White River Junction, Vermont, and professor of psychiatry in the Department of Psychiatry and Pharmacology at Dartmouth Medical School, in Hanover, NH.

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Please direct all correspondence to: Matthew J. Friedman, MD, PhD, National Center for PTSD (116D), VA Medical & Regional Office Center, 215 North Main St, White River Junction, VT 05009; Tel: 802-296-5132; Fax: 802-296-5135; E-mail: Matthew.Friedman@Dartmouth.edu.

Table
Medications for PTSD: Indications and Contraindications[15]

Class	Medication	Daily Dose Range (mg)	Indications	Contraindications
SSRIs	Paroxetine*	10–60	Reduce *DSM-IV* B, C, and D Symptoms Produce improvement on CGI Effective treatment for depression, panic disorder social phobia, and obsessive-compulsive disorder Reduce associated symptoms (rage, aggression, impulsivity, suicidal thoughts)	May produce insomnia, restlessness, nausea, decreased appetite, daytime sedation nervousness, and anxiety May produce sexual dysfunction, decreased libido, delayed orgasm, or anorgasmia Clinically significant interactions for people prescribed MAOIs Significant interactions with hepatic enzymes produce other drug interactions
	Sertraline*	50–200		
	Fluoxetine	20–80		
	Citalopram	20–60		
	Fluvoxamine	50–300		
Other serotonergic antidepressants	Nefazodone	200–600	May reduce *DSM-IV* B, C, and D symptoms Effective antidepressants Trazodone has limited efficacy by itself but is synergistic with SSRIs and may reduce SSRI-induced insomnia	May be too sedating, Rare priapism with trazodone Reports of hepatotoxicity associated with nefazodone treatment
	Trazodone	150–600		
Other 2nd-generation antidepressants	Venlafaxine	75–225	Efficacy in PTSD for either drug has not been demonstrated Effective antidepressants	Venlafaxine may exacerbate hypertension Bupropion may exacerbate seizure disorder
	Bupropion	200–450		
MAOIs	Phenelzine	15-90	Reduces *DSM-IV* B symptoms Produces CGI improvement Effective agents for depression, panic, and social phobia Efficacy in PTSD has not been demonstrated for other MAOIs	Risk of hypertensive crisis makes it necessary for patients to follow a strict dietary regimen Contraindicated in combination with most other antidepressants, CNS stimulants, and decongestants Contraindicated in patients with alcohol/substance abuse/dependency May produce insomnia, hypotension, anticholinergic and severe liver toxicity
TCAs	Imipramine	150–300	Reduces *DSM-IV* B symptoms Produces CGI improvement Effective antidepressant and antipanic agents Desipramine ineffective in one randomized clinical trial Other TCAs have not been tested in PTSD	Anticholinergic side effects (dry mouth, rapid pulse, blurred vision, constipation) May produce ventricular arrhythmias May produce orthostatic hypotension, sedation, or arousal
	Amitriptyline	150–300		
	Desipramine	100–300		

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Table
Medications for PTSD: Indications and Contraindications[15] (cont)

Class	Medication(s)	Daily Dose Range	Indications	Contraindications
Antiadrenergic agents	Propranolol Prazosin Clonidine Guanfacine	40–160 6–10 0.2–0.6 1–3	Reduces *DSM-IV* B and D symptoms Increases CGI improvement Prazosin shown to have marked efficacy for PTSD nightmares and insomnia	May produce hypotension or bradycardia Must be used cautiously in hypotensive patients Titrate prazosin starting at 1 mg at bedtime and monitor blood pressure Propranolol may produce depressive symptoms, psychomotor slowing, or bronchospasm
Anticonvulsants	Carbamazepine	400–1,600	Effective on *DSM-IV* B and D symptoms Effective in bipolar affective disorder Possibly effective in reducing aggressive behavior	Neurological symptoms, ataxia, drowsiness, low sodium, leukopenia
	Valproate	750–1,750	Effective on *DSM-IV* C and D symptoms Effective in bipolar affective disorder	Gastrointestinal problems, sedation, tremor, and thrombocytopenia Valproate is teratogenic and should not be used during pregnancy
	Gabapentin Lamotrigine Topiramate	300–3,600 50–400 200–400	Efficacy of gabapentin, lamotrigine, and topiramate has not been demonstrated in PTSD	Gabapentin—sedation and ataxia Lamotrigine—Steven's-Johnson syndrome, skin rash, and fatigue Topiramate—glaucoma, sedation dizziness, and ataxia
Benzodiazepines	Clonazepam Alprazolam	1–8 0.5–6	Not recommended Do not reduce core *DSM-IV* B and C symptoms Effective only for general anxiety and insomnia Other benzodiazepines have not been tested in PTSD	Sedation, memory impairment, ataxia Not recommended for patients with past or present alcohol/drug abuse/dependency because of risk for dependence May exacerbate depressive symptoms Alprazolam may produce rebound anxiety
Atypical antipsychotics	Risperidone Olanzapine Quetiapine	4–16 5–20 50–750	Preliminary data suggest effectiveness against PTSD symptom clusters and aggression May have a role as augmentation treatment for partial responders to other agents	Weight gain with all agents Risk of type II diabetes with olanzapine

*FDA approved for the treatment for PTSD.

PTSD=posttraumatic stress disorder; SSRIs=selective serotonin reuptake inhibitors; *DSM-IV=Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; B symptoms=intrusive recollections; C symptoms=avoidant/numbing; D symptoms=hyperarousal; CGI=Clinical Global Impressions scale; MAOIs=monoamine oxidase inhibitors; CNS=central nervous system; TCAs=tricyclic antidepressants.

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that SSRIs are very effective for PTSD.[17] Research with the SSRI citalopram indicates that the drug is effective in children with PTSD.[18] Open clinical trials with fluvoxamine have also shown favorable results.[9]

Antidepressants

Although second-generation antidepressants are very popular with clinicians, they have not been tested extensively in PTSD and there are no randomized clinical trials supporting their effectiveness. The best evidence from open trials supports the use of nefazodone, which, similar to SSRIs, promotes serotonergic actions.[10,19] Nefazodone is also less likely to cause insomnia or sexual dysfunction than SSRIs. Trazodone, which has limited efficacy as a standalone treatment, has proven very useful as augmentation therapy with SSRIs. Through its serotonergic action it is synergistic with SSRIs while its sedating properties make it a useful bedtime medication that antagonizes SSRI-induced insomnia.[10]

Other second-generation antidepressants, such as venlafaxine and bupropion, cannot be recommended at this time because there is very little data demonstrating their efficacy in PTSD. Because PTSD is often comorbid with major depression and as venlafaxine and bupropion are both effective antidepressants with relatively benign side-effect profiles, some clinicians automatically favor them over older agents despite the fact that both monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) have proven efficacy in PTSD whereas venlafaxine and bupropion have not.

Monoamine Oxidase Inhibitors

Despite one very successful randomized clinical trial with phenelzine[20] and a quantitative review suggesting that MAOIs produce moderate-to-good global improvement and reduction of reexperiencing symptoms for PTSD patients,[21] these compounds have received little experimental attention since 1990. This lack of attention is probably due to clinician concerns about potentially serious side effects, lack of interest by pharmaceutical companies, and hopes that safer selective MAO-A inhibitors will enjoy wider use.

Certainly, MAOIs are contraindicated for patients who cannot adhere to tyramine-free diets, for patients who cannot abstain from alcohol or many illicit drugs, and for patients prescribed SSRIs, central nervous system (CNS) stimulants, decongestants, or meperidine. Despite this, there remain many patients who might benefit from MAOIs when clinical trials with SSRIs have failed. Before initiating phenelzine treatment, patients should be completely weaned from other antidepressants for at least 7 days (or ≥5 weeks if they had been taking fluoxetine). In addition to their usefulness in PTSD, MAOIs have proven efficacy in depression and panic disorder.

Tricyclic Antidepressants

TCAs are old-fashioned, but potent antidepressants, which, like MAOIs, have not been tested in recent years. The milder side-effect profile of SSRIs and other second-generation antidepressants has undoubtedly contributed to the relative neglect of TCAs, which were once a mainstay of psychopharmacotherapy. Two randomized clinical trials with veterans showed that imipramine and amitriptyline, respectively, produced global improvement and reduced reexperiencing symptoms in veteran subjects[20,22] although a third trial with desipramine was negative.[23] In the one head-to-head comparison between imipramine and phenelzine, the MAOI was more effective although the TCA was still superior to placebo.[20] Side effects associated with TCAs are well-known and can often be managed successfully, but sometimes are the cause of noncompliance or discontinuation. One clear advantage of TCAs and MAOIs over newer antidepressants is their lower cost, which may be a crucial consideration for some patients.

Antiadrenergic Agents

One of the earliest and best established findings in PTSD research is the excessive adrenergic reactivity among patients with the disorder.[24] Despite this robust experimental finding, and despite open trials dating back to 1984,[10] antiadrenergic medications have been largely neglected until recently. All of the agents listed in the Table are safe medications that have been used for many years in treating cardiovascular disease, especially hypertension and cardiac arrhythmias. Although all agents listed achieve the end result of reduced adrenergic activity, they do it via three different mechanisms of action: Propranolol is a postsynaptic β-adrenergic antagonist; prazosin is a postsynaptic α_1 receptor antagonist; and clonidine and guanfacine are presynaptic α_2-receptor agonists which reduce the amount of norepinephrine released into the synaptic cleft.

The best research on this class of agents has focused on prazosin, which has produced marked reduction in traumatic nightmares, improved sleep, and global improvement among veterans with PTSD.[25] Propranolol has been tested in sexually and/or physically abused children with chronic PTSD and produced significant reduction in reexperiencing and arousal symptoms.[26] Because of laboratory research suggesting that propranolol might reduce sympathetic arousal and the encoding of highly charged emotional memories during the immediate aftermath of a traumatic event,[27,28] propranolol was administered prospectively to emergency room patients to see whether it might prevent the later development of PTSD. Although the trend toward lower rates of PTSD was nonsignificant 3 months later, patients who had received an acute 10-day course of propranolol exhibited significantly less sympathetic nervous system hyper-reactivity at the 3-month follow-up assessment.[29]

Clonidine and guanfacine are especially interesting agents because of laboratory evidence that disinhibition of adrenergic neurons with the α_2-adrenergic antagonist yohimbine, produces panic attacks, dissociative symptoms, and PTSD flashbacks among combat veterans with this disorder.[24] Since both clonidine and guanfacine directly oppose the actions of yohimbine, there is a rationale to suggest that they might be especially effective clinically for patients in whom dissociation and flashbacks figure prominently. While there are a number of clinical trials currently exploring this possibility, it is merely speculation at this point.

Clonidine has also been used successfully with Southeast Asian refugees with PTSD both as a supplement to antidepressant treatment or by itself. Indeed, it has been reported that in many cases, these refugees prefer clonidine to any other medication and can be maintained for years on clonidine alone.[30]

Anticonvulsants

An important neurobiological model for PTSD is that certain brain nuclei become sensitized or "kindled" following exposure to traumatic events. Such a model which led to the successful use of carbamazepine and valproate in the treatment of bipolar affective disorder has also been proposed for PTSD.[31,32] Unfortunately, there have been no randomized trials with either anticonvulsant involving PTSD patients, although promising open trials with both medications have been reported.[10] As shown in the Table, both agents have effectively reduced hyperarousal symptoms. Carbamazepine appears to reduce reexperiencing and aggressive symptoms while valproate has been more effective in reducing avoidant/numbing symptoms. Both of these medications have many potential side effects and are not always well tolerated by patients. The major concerns with carbamazepine are neurological symptoms, hyponatremia, and bone marrow suppression resulting in leukopenia. Valproate is teratogenic and contraindicated for women who plan to become pregnant, since its disruption of fetal development occurs early in the first trimester. Therefore, it is best to discontinue this medication before pregnancy begins. Impaired liver function and thrombocytopenia may also occur with valproate. In short, the complexities of clinical management with these effective anticonvulsants have shifted current attention to newer agents (eg, gabapentin, lamotrigine, and topiramate) which have yet to be tested systematically with PTSD patients.

Lithium

Although lithium's properties are well established both as an antikindling agent and as an effective agent for recurrent affective disorders, it has received little attention as a treatment for PTSD. Indeed, with the exception of two small series of open-label case reports published approximately 20 years ago,[33] there has been no systematic investigation of lithium with respect to PTSD. In the aforementioned clinical trials, lithium reportedly reduced autonomic arousal, irritability, aggression, anxiety, insomnia, alcohol consumption, and capacity to cope with stress. Due to lack of research in PTSD, lithium cannot be recommended as treatment for PTSD at this time.

Benzodiazepines

Because of their proven efficacy as anxiolytics, benzodiazepines are often prescribed for PTSD. This is unfortunate because studies with alprazolam and clonazepam indicate that these agents have no proven efficacy against core PTSD symptoms,[10,34] while there are many more effective nonbenzodiazepine agents available. In PTSD, benzodiazepines can be expected to improve sleep and reduce general anxiety but not to have any salutary impact on the syndrome itself. Furthermore, there are potential risks of prescribing these agents because they may exacerbate depressive symptoms, produce CNS depression, or be problematic for patients with past or present alcohol/drug misuse. In addition, alprazolam may produce rebound anxiety, which is poorly tolerated by PTSD patients.

Antipsychotic Agents

When PTSD first burst upon the clinical scene in the 1970s with Vietnam veterans seeking treatment at VA hospitals, many conventional antipsychotic agents were prescribed to ameliorate intense hyperarousal, hypervigilance, dissociative symptoms, aggressivity, and reexperiencing symptoms. It is now understood that these PTSD symptoms have a very different pathophysiology than psychotic disorders and that there are much more effective treatments available. In addition, the many side effects, especially extrapyramidal symptoms, make these agents a poor choice for PTSD treatment. Conventional antipsychotics are not recommended for PTSD patients.[10]

In contrast, atypical antipsychotic agents, which have potent pharmacologic actions, have a less toxic side-effect profile. Although there are very little data from clinical trials, preliminary studies with atypical antipsychotics suggest that they may be effective agents for PTSD global improvement, selective action on *DSM-IV* B (intrusive recollections), C (avoidant/numbness), or D (hyperarousal) symptoms, and on aggressive behavior.[10] Atypical agents may have a unique niche as augmentation treatment for partial responders to SSRIs or other first- or second-line agents, especially for patients with intense hypervigilance/paranoia, agitation, dissociation, or brief psychotic reactions associated with their PTSD.[35] As for side effects, all atypicals may produce weight gain and olanzapine treatment has been linked to the onset of type II diabetes mellitus.

A General Approach to Pharmacotherapy

Pharmacotherapy is only one of several treatment options for PTSD patients, especially in view of the great success of cognitive-behavioral therapy (CBT).[36] Medication may be a good choice when patient acceptability of such an approach is high, when comorbid conditions are present that are responsive to pharmacotherapy (eg, depression, panic disorder, social phobia, and obsessive-compulsive disorder), or when CBT treatment is unavailable.[9]

At this time, SSRIs must be considered first-line treatment for PTSD. For patients who exhibit a partial response to SSRIs, one should consider continuation or augmentation.[37] A recent trial with sertraline showed that approximately half of all patients who failed to exhibit a successful clinical response after 12 weeks of sertraline treatment, did respond when SSRI treatment was extended for another 24 weeks.[38] Practically speaking, clinicians and patients will usually be reluctant to stick with an ineffective medication for 36 weeks, as in this experiment. Therefore, augmentation strategies seem to make sense. Here are a few suggestions based on clinical experience and pharmacologic estimates, rather than on hard evidence:[16]

Excessively aroused, hyperreactive, or dissociating patients might be helped by augmentation with an antiadrenergic agent; labile, impulsive, and/or aggressive patients might benefit from augmentation with an anticonvulsant; and fearful, hypervigilent, paranoid, and psychotic patients might benefit from an atypical antipsychotic.

Conclusion

SSRIs are first-line treatments for PTSD due to their broad spectrum effects against all PTSD symptom clusters, their efficacy against many comorbid disorders, and their effectiveness against associated symptoms, such as impulsivity, aggression, and suicidal thoughts.[9,10] Patients who cannot tolerate SSRIs or who show no improvement might benefit from MAOIs, TCAs, or the antidepressant nefazodone. (Venlafaxine and bupropion

cannot be recommended because they have not been tested systematically in clinical trials).[16] Evidence favoring the use of these agents is not as compelling as for SSRIs because many fewer subjects have been tested at this point.

There is a strong rationale from laboratory research to consider antiadrenergic agents and it is hoped that more extensive testing will establish their usefulness for PTSD patients. In addition, despite suggestive theoretical considerations and clinical findings, there is only a small amount of evidence to support the use of carbamazepine or valproate with PTSD patients. Research with other anticonvulsants is at a preliminary stage.

Benzodiazepines cannot be recommended for PTSD patients as they do not appear to have efficacy against core PTSD symptoms. In addition, neither conventional antipsychotics nor lithium can be recommended for PTSD patients. Preliminary results suggest, however, that atypical antipsychotics may be useful, especially to augment treatment with first- or second-line medications, although much more research is needed.

Although we have just scratched the surface in our search for effective agents for PTSD, different pharmacologic agents will surface as potential treatments for PTSD as we learn more about the pathophysiology of the disorder. Some agents, such as corticotropin-releasing factor antagonists and substance P antagonists, are beginning to be tested while others are still on the drawing board.[6] We can all look forward to exciting future developments in the treatment of PTSD. **PP**

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